Planning for Successful, Efficient, Pharmaceutical Product Development

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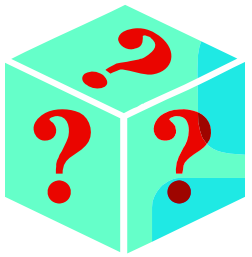
How to become efficient and successful?



- Why is *efficiency* important to success?
- Who are we and how to we interact?
- What is the process for review?
- How can it be better?
- Why and how do we do what we do?

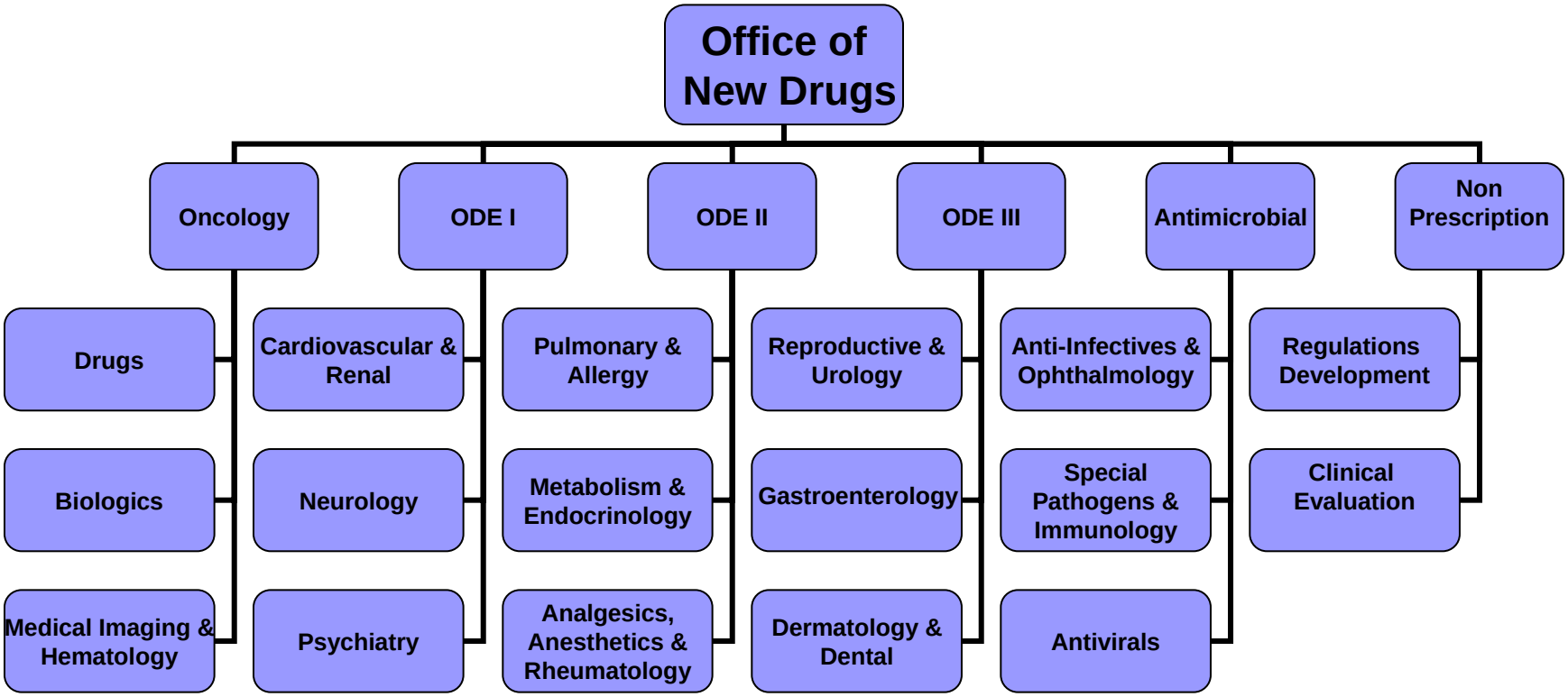
Why are effective interactions important?

- Shared Public Health goal
  - FDA Mission: protecting and "…*advancing* the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable…"
- FDA has expertise and "insider" knowledge; we are uniquely positioned to improve drug development and review

What we have found…

- Historically, approximately 75% of NME NDAs are eventually approved but most require multiple cycles (inefficient)
- First cycle review performance report
  - *"Emphasis on implementation should, in particular, be placed on less-experienced sponsors who seem to be at greatest risk for multiple cycle review. Earlier and more effective communication with sponsors...will maximize the potential to identify and communicate issues and develop a resolution plan in a timely manner."*

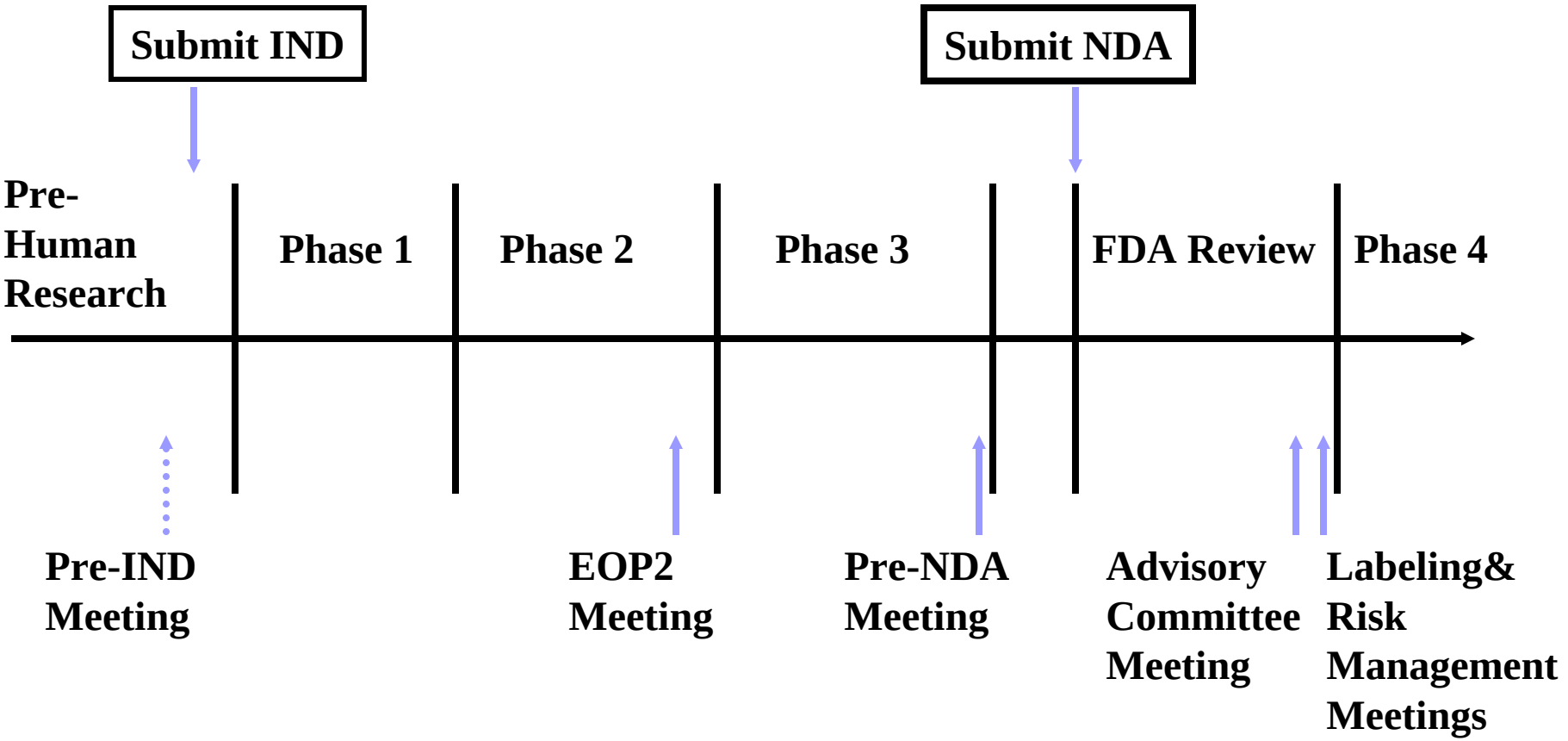
Who we are…


Office of New Drugs
Oncology
ODE I
ODE II
ODE III
Antimicrobial
Non Prescription
Drugs
Biologics
Medical Imaging & Hematology
Cardiovascular & Renal
Neurology
Psychiatry
Pulmonary & Allergy
Metabolism & Endocrinology
Analgesics, Anesthetics & Rheumatology
Reproductive & Urology
Gastroenterology
Dermatology & Dental
Anti-Infectives & Ophthalmology
Special Pathogens & Immunology
Antivirals
Regulations Development
Clinical Evaluation

Review teams: Multi-disciplinary experts

- Clinical
  - Including microbiologists for anti-microbials
- Chemistry/manufacturing
  - Including sterility, if needed
- Non-clinical pharmacology/toxicology
- Clinical pharmacology/biopharmaceutics
- Statistics
- Regulatory (Project Manager)

Drug development and review – where does it begin?

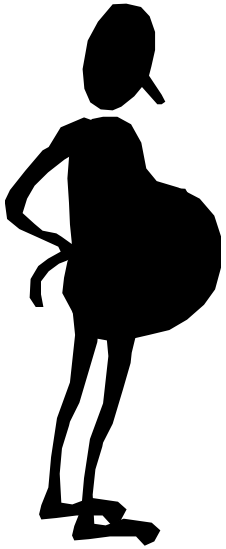


When is an IND required?

- Generally whenever studies in humans are conducted in the U.S.
- Exemptions:
  - Drug is approved in the U.S. and investigation is not intended to support change in labeling or advertising and does not change the known risk/benefit profile
  - Some bioavailability/bioequivalence studies
  - Still need IRB approval and informed consent

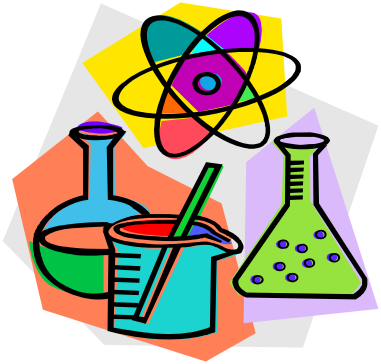
Pre-IND Meeting

- Not necessary for every IND
- Focus on pre-clinical studies and design of initial clinical protocol
- Opportunity to discuss uniqueness of molecular entity, studies or indications
- Pre-IND meeting ≠ no clinical hold
- ☺ Ask specific, answerable questions
- ☺ Remember: advice given is based on information provided



Basic information needed – IND application

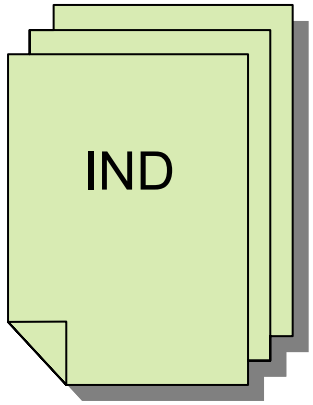
- Preclinical
  - Enough data to support proposed clinical protocol
  - Basic exposure data
- Chemistry, manufacturing and controls
  - Sufficient information to assure proper id, quality, purity and strength
  - Sufficient information to assess whether batches can be adequately produced and consistently supplied



Basic information needed – IND application

- Clinical trial protocol
  - Determine the phase of development
  - Provide supporting data (e.g., from ex-U.S. trials, PK data)
  - Specify how to ensure safety of the subjects/patients in the study
  - Utilize a step-wise approach – build on what you know…..

New IND submission



- Content
- Process
  - Paper unless in eCTD format (ICH)
  - Evaluated by appropriate review staff
- Actions (within 30 days)
  - “Reasonably safe to proceed” = active
  - Clinical hold (partial or full)

Active IND = Drug Development!

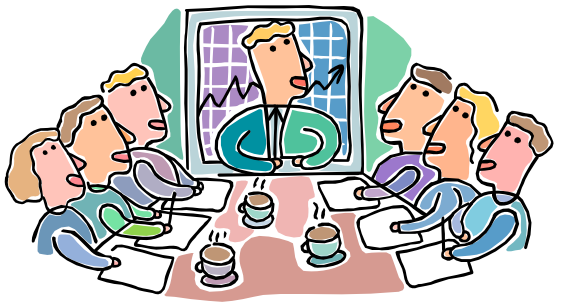
- New trials can be initiated once protocol is submitted and IRB approval is obtained – no waiting!
- Amendments include clinical protocol changes, new protocols, information amendments of preclinical data, chemistry, etc.
- Safety and annual reports required
- ☺ Clearly identify all submissions (e.g., stability protocol)

Review of Active INDs

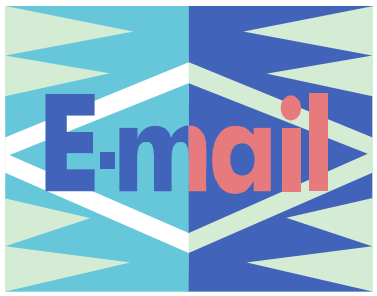
- Review builds as development continues
- An active IND can be placed on clinical hold or partial clinical hold at *any time*
- Sponsors may not promote investigational drugs or uses, and may not charge for investigational drugs (unless specifically approved by FDA)
- Housekeeping: inactive, withdrawal, termination

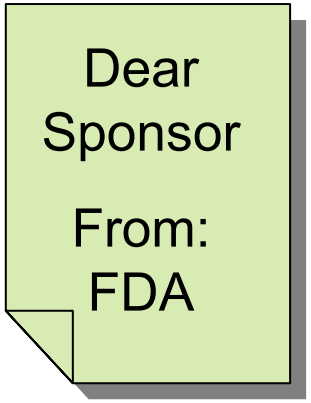
IND Interactions

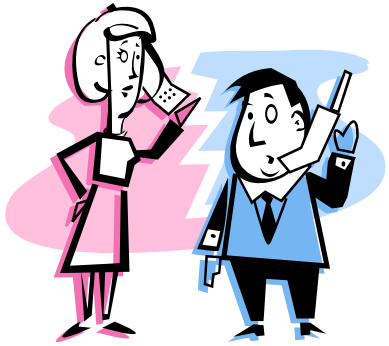
- Meetings
  - End of Phase 2
  - Pre-NDA
  - Guidance/Advice



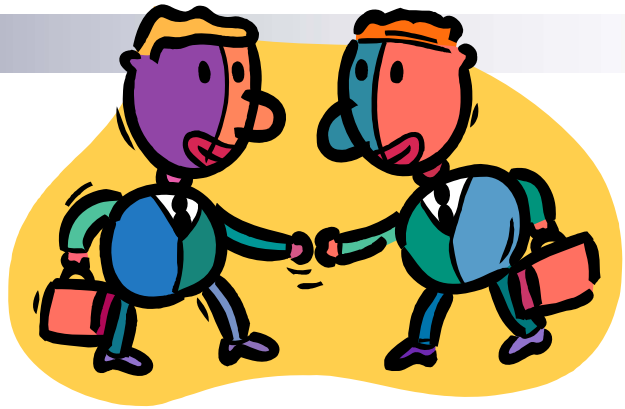
- Correspondence and verbal communication







Key Meetings – End of Phase 2



- Held after Phase 1 and 2 studies are complete
- Discuss and reach agreement on clinical studies that will provide definitive support for efficacy and safety
- ☺ Most important meeting during development!
- ☺ Be honest about possible problems identified during development
- ☺ Mock-up a label so we can help ensure that your trial design supports your labeling goals

Key Meetings – Pre-NDA

- Request when all studies designed to support the desired claims of safety and efficacy have been completed
- Discuss whether evidence of effectiveness was seen in the Phase 3 trials, the need for risk management, technical aspects (format), plans to address potential problem areas
- ☺ Address all previous advice not taken, and unresolved issues
- ☺ Be honest – are you really ready to submit?

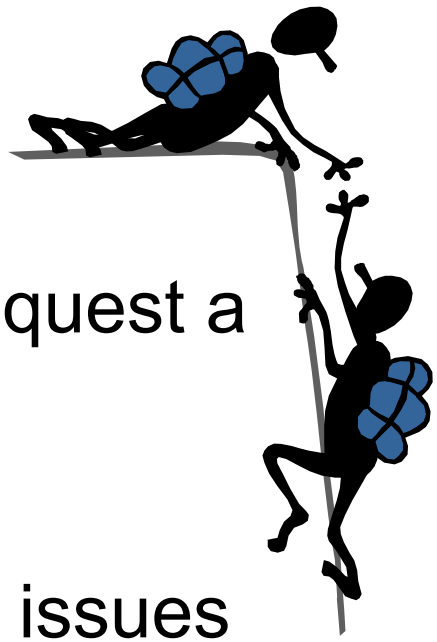
Other interactions – Guidance/Advice

- Guidance meetings can be held at request of sponsor or FDA to discuss any issues
- Written feedback can be provided upon request for amendments to the IND (not always provided)
- Regulatory and procedural advice can be given over the phone or by e-mail
- ☺ Keep in touch with the Regulatory Project Manager on an informal basis – provide updates, “Heads up!”, etc.
- ☺ Never assume – be clear

Meetings are critical – Here are a few reminders…

- **Rule #1** – follow the guidance!
- Submit requests in writing
- Don't forget - telecons are meetings too
- Minutes for all meetings are provided in 30 days
  - FDA version is "official" – submit disagreements in writing

Meetings are critical – Helpful Hints!



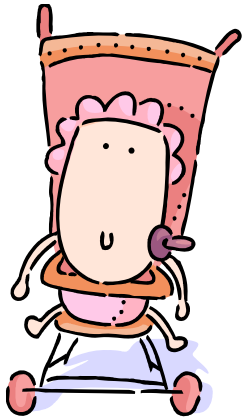
- ☺ Identify your questions before you request a meeting
- ☺ Don't ask unanswerable questions
- ☺ Select attendees based on identified issues
- ☺ Don't hide concerns – share them and propose solutions
- ☺ Skip the presentation – use the time for discussion

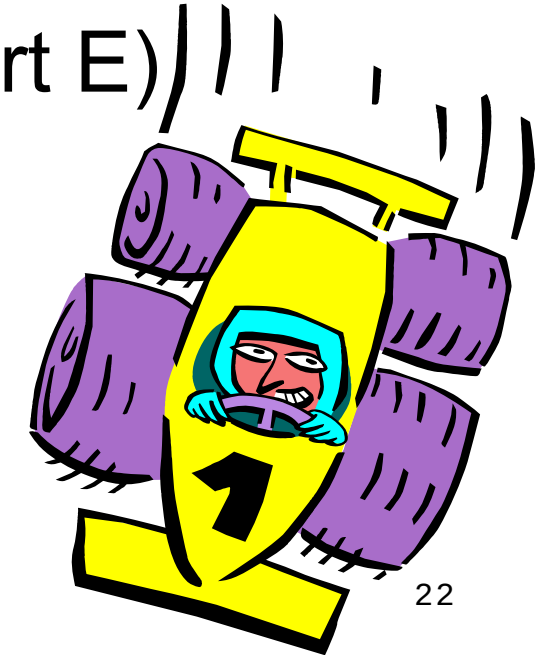
Meetings are critical – More Helpful Hints!

- ☺ Stay focused on the agenda
- ☺ Minimize surprises
- ☺ Stay professional
- ☺ Listen closely and strongly consider what is being recommended
- ☺ Have someone (either you or FDA) summarize the outcome and any action items

Special Programs – Drug Development

- Emergency IND
- Pediatric Research Equity Act
- Treatment IND
- Subpart E (21 CFR 312 Subpart E)
- Fast track
- Special Protocol Assessment
- End of Phase 2a meetings





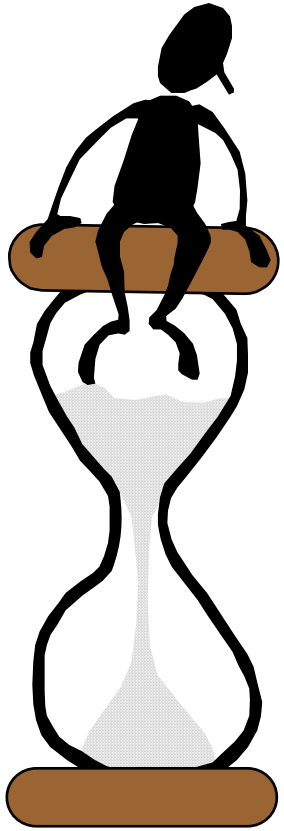
Development Complete – May You Market?

- NDA/BLA submission User Fees
  - Current fee: $767,400
  - Small Business Waiver!!

- Review classification:
  - priority or standard
  - Chemical class
  - 505(b)(1) or 505(b)(2)

- Filing review

Application Filed – Now what?

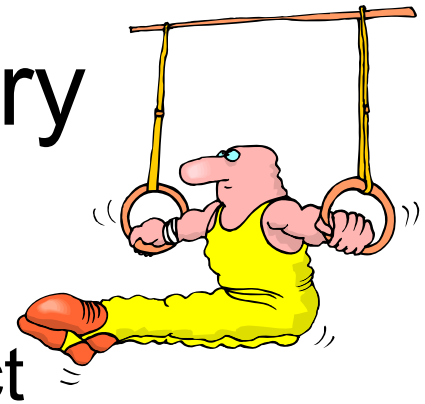


- Guidance for Review Staff and Industry: Good Review Management Principles and Practices
- Primary review, consults ongoing…
- Requests for additional information via telephone, facsimile, IR and DR letters
- Labeling negotiations later in the review cycle

Advisory Committee Meetings – Should you worry?

- Opportunity to gain input from experts in the field
- Often held for new molecular entities, particularly for first in class products, first in class Rx to OTC switches, new indications, risk management planning, controversial products, specific safety or efficacy concern
- Applicant can request but Agency must concur
- Recommendations are advisory only and not binding

How to prepare for an Advisory Committee meeting

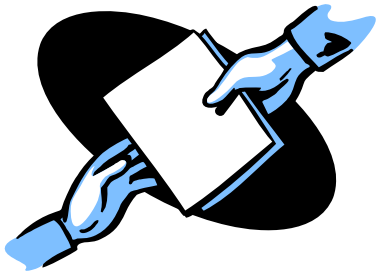


- Work closely with the Regulatory Project Manager and Advisors and Consultants Staff
- Be aware of requirements and timelines for information disclosure
- If you haven't been, watch one in advance (in person or via commercially available sources) to familiarize yourself with the typical format
- ☺ Remember that the press will usually be present
- ☺ Open public hearing time is dependent upon the topic

How does the review end?

Approval

Approvable



Not Approvable

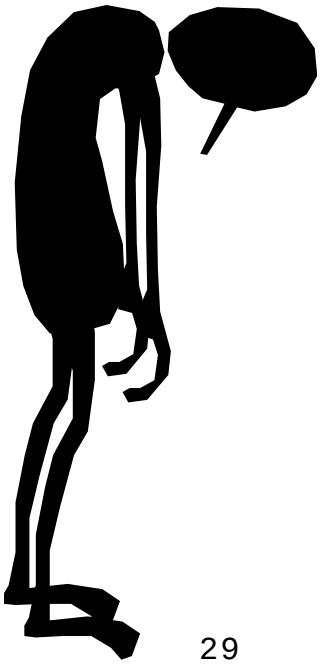
Coming soon –
Complete Response

Special Programs – Marketing Application Review

- Accelerated approval (Subpart “H”)
- Rolling review
- Continuous Marketing Application Pilot 1
- Best Pharmaceuticals for Children Act

What to do if you are not approved in the first review cycle…

- Request an end-of-review meeting with the signatory authority to ensure clear understanding of deficiencies and information needed to resolve them
- Resubmit!
  - Class 1/Class 2 resubmissions
  - No additional user fee



Reality Check

- Complications…Reorganization and Move!
- Each reviewer has multiple applications at any given time
- ☺ "Do your homework" in advance of calling
- ☺ Discuss an approach with the RPM for communications to balance the "tension" of constant calls vs. information voids

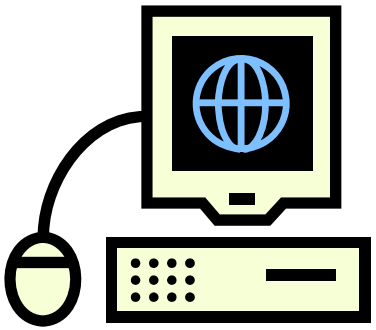
- Start with the Regulatory Project Manager
- Follow the chain of command
- Scientific, regulatory, procedural disputes above the Division follow formal dispute resolution
- Utilize the Ombudsman's office

Helpful Resources (*Why* FDA does what it does…)

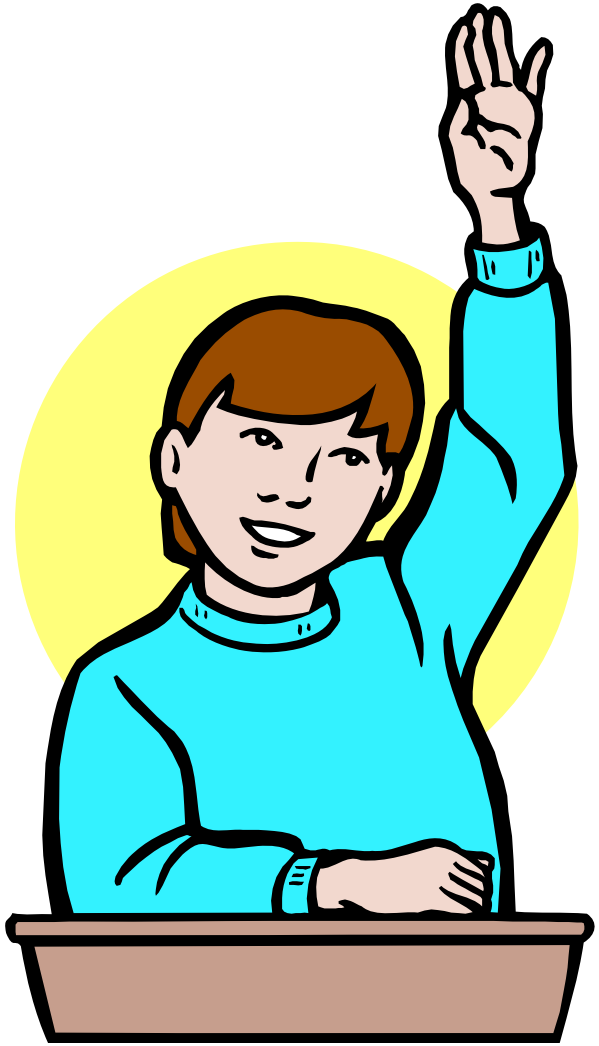
- Legislation (FD&C Act, PDUFA, FOIA, FACA, PREA, BPCA, and many more)
- Regulations CFR Title 21
  - 50 Human Subject Protection
  - 54 Financial Disclosure
  - 56 Institutional Review Boards
  - 201 Labeling
  - 312 IND
  - 314 NDA

Helpful Resources (*How* FDA does what it does…)

- Guidances
  - Current Agency thinking to Industry; some directed to review staff
- Manual of Policy and Procedures (MAPPs)
  - Internal processes
- Where to go?
  - www.fda.gov/cder



Questions?



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